II. REMARKS

Formal Matters

Claims 1, 2, 4, 7-11, and 18-20 are pending after entry of the amendments set forth herein.

Claims 1, 2, 4, 7-11 and 18 were examined and were rejected. Claims 12-17 were withdrawn from consideration.

Claims 2, 4, and 7 are amended. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as an acquiescence to any objection or rejection of any claim. Claims 2 and 4 were amended to delete reference to SEQ ID NO:06, as suggested in the final Office Action. Support for the amendments to claim 7 is found in the claims as originally filed, and throughout the specification, in particular at the following locations: claim 7 as originally filed; and page 5, lines 23-28. Accordingly, no new matter is added by these amendments.

Claims 14-17 are canceled without prejudice to renewal, without intent to acquiesce to any rejection, and without intent to surrender any subject matter encompassed by the canceled claims. Applicants expressly reserve the right to pursue any canceled subject matter in one or more continuation and/or divisional applications.

Claims 19 and 20 are added. Support for new claims 19 and 20 is found in the claims as originally filed, and throughout the specification, in particular at the following locations: claim 19: page 9, lines 11-16; claim 20: page 21, lines 12-15.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Examiner Interview

The undersigned Applicants' representative thanks Examiner Kemmerer and Examiner Bunner for the courtesy of a telephonic interview, which took place on October 9, 2003, and which was attended by Examiners Kemmerer and Bunner, inventor Dr. Aaron Hsueh, and Applicants' representative Paula A. Borden. During the interview, the utility rejection of the claims under 35 U.S.C.§101 was discussed.

Sequence compliance

The Office Action stated that the application fails to comply with the sequence listing requirements of 37 C.F.R.§§1.821-1.825. The Office Action stated that the sequences disclosed in Figures 5 and 6 are not accompanied by the required reference to the relevant sequence identifiers.

Applicants submit herewith Replacement Figures 5 and 6A-6C, which replacement figures include sequence identifiers that correspond to sequence identifiers submitted in the sequence listing filed along with the amendment, filed on February 3, 2002 and responsive to the November 6, 2002 Office Action.

Claim objections

The Office Action stated that claims 1, 2, 4, and 7 are objected to because these claims recite non-elected groups. The Office Action suggested amending claims 1, 2, 4, and 7 to remove reference to SEQ ID NOs:5 and 6.

Applicants' position on this issue has been made of record in the amendment, filed on February 3, 2002 and responsive to the November 6, 2002 Office Action. Without conceding as to the correctness of this objection, claims 2, 4, and 7 are amended to delete reference to SEQ ID NOs:5 and 6.

Rejection under 35 U.S.C.§101 and §112, first paragraph

Claims 1, 2, 4, 7-11 and 18 were rejected under 35 U.S.C.§101 as allegedly lacking utility.

The Office Action stated that the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility. Applicants respectfully traverse the rejection.

The specification provides a credible, specific and substantial utility for the claimed polynucleotides.

1) The specification asserts that the human LGR7 polypeptide is a novel mammalian G protein coupled receptor (GPCR), characterized by the presence of extracellular leucine rich repeat regions. The specification asserts that the LGR7 polypeptide functions as a GPCR. Specification, page 3, lines 26-29.

2) The specification states that nucleic acids encoding mammalian LGR7 polypeptides are useful for producing LGR7 polypeptides, which polypeptides are asserted to function as GPCR. Specification, page 9, lines 20-27.

3) The specification states that the ***LGR7 ligand is a hormone***. Specification, page 21, lines 12-15.

4) The specification states that the extracellular domain can be solubilized ***and used to neutralize the activity of the endogenous ligand*** (e.g., a hormone.) Specification, page 11, lines 3-4; and page 21, lines 12-15.

5) The specification further states that the LGR7 polypeptides are useful for identification of a ligand for the GPCR; for screening for agonists and antagonists. Specification, page 11, lines 1-4; page 20, lines 8-14; and page 2, lines 13-14.

The claimed polynucleotides are thus useful for producing LGR7 polypeptides, which polypeptides are hormone receptors, and are useful for screening for agonists and antagonists, and for the generation of functional binding proteins for the neutralization of the action of an endogenous ligand. Thus, the specification provides a number of additional credible, specific and substantial utilities for the claimed polynucleotides.

LGR-type GPCR share features not shared by the majority of GPCR.

As discussed during the Examiner Interview, the LGR-type GPCR are not like other (non-LGR-type) GPCR. First, the LGR disclosed in the instant application include, in addition to the 7 transmembrane structure typical of other GPCR, a leucine-rich extracellular domain at the amino terminus of the protein. Specification, page 3, line 30 to page 4, line 1. This amino-terminal extracellular domain with leucine-rich repeats is referred to in the specification as an "ectodomain" to emphasize the fact that it is extracellular. Specification, page 25, lines 18-19. As illustrated in Figure 6 of the instant application, the LGR-7 ectodomain is over 300 amino acids in length; the leucine rich repeat portion of the ectodomain is approximately 200 amino acids in length; and the 7 transmembrane region is approximately 250 amino acids in length. Thus, the ectodomain has nearly the same length as the 7 transmembrane portion. Other than the LGR-type GPCR, no other GPCR has such an ectodomain. This striking difference is illustrated in the accompanying figure entitled "Schematic presentation of functional domains in LGR family receptors," provided herewith as Exhibit 1.

Other than LGR-type GPCR, GPCR typically ***do not have*** an amino-terminal ectodomain that can be expressed as soluble proteins and used to neutralize the activity of an endogenous hormone ligand. This particular asserted utility of LGR-type GPCR is thus *specific* to LGR-type GPCR.

As illustrated on the world wide web site receptome.stanford.edu, there are **hundreds** of GPCR with the typical 7 transmembrane structure. In contrast, fewer **than 10** mammalian LGR-type GPCR had been identified as of the priority date of the instant application.

As discussed during the Examiner Interview, the disclosed LGR-type GPCR have an overall structure that is very similar to luteinizing hormone receptor (LHR), follicle stimulating hormone receptor (FSHR; also referred to in the art as "follitropin receptor"), and thyroid stimulating hormone receptor (TSHR). Specification, page 3, lines 29-30. LHR, FSHR, and TSHR were known in the art as of the priority date of the instant application. ***All three are hormone receptors***. The relationship between LGR-type GPCR and other GPCR, and among LGR-type GPCR, is illustrated in Figure 3 of Hsu et al. ((2000) *Molec. Endocrinol.* 14:1257-1271; "Hsu (2000)", a copy of which was provided as Exhibit 2 in the amendment filed on February 3, 2003.

As discussed during the Examiner Interview, the analysis of LGR7 was conducted based on its structural similarity to human LHR, FSHR, and TSHR. As discussed in Hsu (2000), features of the LGR7 could be identified based on the structural similarity to LHR. Hsu (2000) states that, based on an alignment of the LGR7 amino acid sequence with those of LHR and TSHR, two different point mutations were made in LGR7 that affected its function as a GPCR. Hsu (2000), page 1261, column 2, second full paragraph, to page 1263, column 2, end of Results section. Thus, the function of LGR-7 was determined based on its close structural similarity to LHR and TSHR.

The fact that LGR7 bears a close structural relationship to the previously known LGR-type GPCRs LHR and TSHR is illustrated in the alignments provided herewith as Exhibit 2-4. Exhibit 2 provides an amino acid sequence alignment of LGR7 with LHR. Exhibit 3 provides an amino acid sequence alignment of LGR7 with TSHR. Exhibit 4 provides an amino acid sequence alignment of LGR7 with TSHR, which alignment shows the locations of leucine-rich repeats (LRR), and highlights the sequence similarities between the two proteins.

The data presented in Hsu (2002) provide further evidence for the fact that, as asserted in the specification, LGR-7 is a GPCR and binds a hormone.

As discussed during the Examiner Interview, the disclosed LGR-7 polypeptide, like LHR, FSHR, and TSHR, binds a hormone, functions as a GPCR, and has signal transduction properties similar to those of LHR. ***The specification discloses that LGR-7 is a hormone receptor***. Specification, page 21, lines 12-15.

The fact that the instant claims are supported by a credible, specific and substantial utility is further demonstrated in Hsu et al. ((2002) *Science* 295:671-674; "Hsu (2002)", a copy of which was provided as Exhibit 1 along with the response filed on February 3, 2003), a publication co-authored by inventors Sheau Y. Hsu and A.J.W. Hsueh. Hsu (2002) states that LGR7 binds the hormone relaxin, and that relaxin activates adenylate cyclase through G_S proteins upon relaxin binding. Hsu (2002), page 672, column 1, last paragraph; and Figure 1. Thus, Hsu (2002) provides further evidence for the fact that, as asserted, LGR-7 functions as a GPCR, and ***is a hormone receptor***.

The data presented in Hsu (2002) provide further evidence for the fact that, as asserted in the specification, the solubilized ectodomain of LGR-7 is useful to neutralize the activity of an endogenous hormone ligand of LGR-7.

As discussed during the Examiner Interview, solubilized LGR-7 ectodomain is useful to neutralize the activity of the endogenous hormone ligand of LGR-7. The specification asserts that the ectodomain of LGR-7 can be used to neutralize the activity of an endogenous hormone ligand of LGR-7. Specification, page 21, lines 12-15. As discussed above, this particular utility is specific to LGR-type GPCR, i.e., it would not apply to *any* GPCR.

Hsu (2002) states that 7BP, a soluble ectodomain of LGR7, antagonizes the action of the endogenous hormone ligand of LGR-7, i.e., relaxin. Hsu (2002), page 673, Figure 4; and column 2. Thus, Hsu (2002) demonstrates that LGR7 is useful for the generation of functional binding proteins that neutralize the action of an endogenous hormone ligand of LGR-7.

In summary, the instant specification provides a credible, substantial, and specific utility for the claimed nucleic acids. In view of such, the rejection of claims 1, 2, 4, 7-11, and 18 under 35 U.S.C.§101 may be withdrawn. Furthermore, and as discussed in more detail below, because the specification discloses a credible, substantial, and specific utility for the claimed nucleic acids, those skilled in the art would know how to use the claimed nucleic acids. Accordingly, the rejection of claims 1, 2, 4, 7-11, and 18 under 35 U.S.C.§112, first paragraph, may be withdrawn.

Applicants submit that the rejection of claims 1, 2, 4, 7-11 and 18 under 35 U.S.C. §101 has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C.§112, first paragraph

Claims 1, 2, 4, 8-11, and 18 were rejected under 35 U.S.C.§112, first paragraph, as allegedly lacking enablement. Claims 1, 2, 4, 8-11, and 18 were rejected under 35 U.S.C.§112, first paragraph, as allegedly lacking written description.

Enablement

The Office Action stated that the specification does not teach LGR7 nucleic acid variants or polypeptide variants. The Office Action further stated that the specification does not teach any functional or structural characteristics of the variants or fragments of the nucleic acid of SEQ ID NO:07 or the polypeptide of SEQ ID NO:08. Applicants respectfully traverse the rejection.

The specification does indeed teach LGR7 nucleic acid and polypeptide variants.

The specification discusses various polypeptide fragments of LGR7. Specification, page 9, line 5 to page 11, line 17. Furthermore, the specification provides the nucleotide and amino acid sequences of at least two LGR7 polypeptides. As shown in Figure 5, the polynucleotides identified as SEQ ID NO:05 and SEQ ID NO:07 encode the polypeptides identified as SEQ ID NO:06 and 08, respectively. Both SEQ ID NO:06 and 08 are LGR7 polypeptides. The specification states that the LGR7 polypeptides are encoded by splice variants. Specification, page 25, lines 15-25.

The specification teaches fragments of LGR7 and discusses the functional characteristics of such fragments.

The specification discusses the extracellular domain of LGR7, and states that this ectodomain is useful, e.g., in the neutralization of the action of endogenous ligands. Specification, page 11, lines 1-4; and page 21, lines 12-15. The specification discusses the structure of LGR7, and states that LGR7 contains a leucine-rich repeat-containing ectodomain. Specification, page 25, lines 15-19. Figure 6 of the instant application shows an alignment of LGR4, LGR5, LHR, FSHR, and TSHR, and shows the position of the ectodomain. It would require nothing more than the skill of one ordinarily skilled in the art to include LGR7 in the alignment to determine the ectodomain. Indeed, Hsu (2002) did just that, and generated a soluble LGR7 ectodomain. As discussed above, Hsu (2002) demonstrated that a soluble extracellular domain of LGR7 functions as an antagonist to LGR7, neutralizing the action of the ligand relaxin. Thus, those skilled in the art, given the guidance in the specification, would know which fragments of LGR7 would be expected to function as discussed in the specification.

Based on the guidance in the specification, those skilled in the art could make variants of LGR7 and predict their function.

Based on the alignments provided in Figure 6, those skilled in the art could readily determine, without undue experimentation, those amino acids of LGR7 that could be altered without changing the function of LGR7, and those amino acid residues that could be altered to result in a change of LGR7 function. The fact that those skilled in the art could readily identify amino acid residues essential for function is demonstrated in Hsu et al. (2000). Hsu (2000) states that, based on an alignment of the LGR7 amino acid sequence with those of other hormone-binding GPCR, point mutations were made in LGR7 that affected its function as a GPCR. Hsu (2000), page 1261, column 2, second full paragraph, to page 1263, column 2, end of Results section. Thus, given the information provided in the instant specification, those skilled in the art could readily and without undue experimentation identify and mutate amino acid residues important for the function of an LGR7 polypeptide as a GPCR.

The final Office Action cited various references to support the assertion that predicting protein and DNA structure from sequence data is problematic. However, as noted above, and as discussed previously, Applicants showed that the amino acid sequence of LGR7 could be aligned with the amino acid sequence of other LGR-type GPCR, and amino acids could be successfully identified that altered the function, or that had no effect on the function, of LGR7. Accordingly, those skilled in the art could,

without undue experimentation, do exactly as Applicants did using nothing more than the information provided in the specification, and identify, make, and use LGR7 variants.

Written description

The Office Action stated that claims 1, 2, 4, 8-11, and 18 contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse the rejection.

The specification provides the nucleotide and amino acid sequences of at least two LGR7 polypeptides. As shown in Figure 5, the polynucleotides identified as SEQ ID NO:05 and SEQ ID NO:07 encode the polypeptides identified as SEQ ID NO:06 and 08, respectively. Both SEQ ID NO:06 and 08 are LGR7 polypeptides. The specification states that the LGR7 polypeptides are encoded by splice variants. Specification, page 25, lines 15-25. Furthermore, as discussed above, the specification provides guidance for various fragments of LGR7 polypeptides, and their uses. Thus, the specification provides adequate written description for the claimed polynucleotides.

The Office Action stated that the description of two LTR7 polynucleotides and polypeptides is not a representative number of embodiments to support the description of an entire genus of functionally equivalent polynucleotides and polypeptides.

The U.S. Patent & Trademark Office's policy on written description is set forth in The Revised Interim Guidelines for Examination of Patent Applications Under 35 U.S.C. §112, paragraph 1 "Written Description" Requirement, (*Federal Register* (Dec. 21, 1999) Vol. 64 (No. 244):71427-71440) ("Revised Guidelines"). As stated in the Revised Guidelines, "In most technologies which are mature, and *wherein the knowledge and level of skill in the art is high*, a written description question should not be raised for original claims even if the specification discloses only a method of making the invention and the function of the invention." Revised Guidelines, page 71436. The written description guidelines are based in part on *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir.1997). It should be remembered that *University of California v. Eli Lilly and Co.*, (Fed. Cir.1997) was based on a patent that was filed in 1977, i.e., over 20 years ago, when the level of skill in the art was not at the level that it was as of the filing date of the instant application.

In view of the high level of skill of those of ordinary skill in the art as of the priority date of the instant application, and in view of the fact that at least two LGR7 polynucleotides were specifically disclosed in the application, instant claims 1, 2, 4, 8-11, and 18 comply with the written description requirement of 35 U.S.C.§112, first paragraph.

Rejection under 35 U.S.C.§112, second paragraph

Claim 7 was rejected under 35 U.S.C.§112, second paragraph, as allegedly indefinite.

The Office Action stated that the phrase "complementary sequence thereof" renders the claim indefinite because it is unclear whether "complementary sequence thereof" refers to the entire nucleic acid sequence complement or variants and fragments of the complement.

Without conceding as to the correctness of this rejection, claim 7 is amended to recite "the complete complementary sequence thereof."

Applicants submit that the rejection of claim 7 under 35 U.S.C. §112, second paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

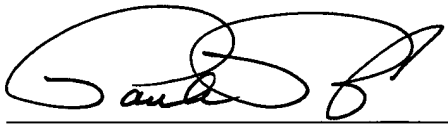
III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN084.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: Oct. 22, 2003

By: 

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